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RELATIVE INCREASE IN CHLORIDE EXCRETION IN THE DOG AFTER GRADUATED DOSES OF MERCURIAL DIURETICS

A PART OF A DISSERTATION SUBMITTED TO THE FACULTY OF THE DIVISION OF THE BIOLOGICAL SCIENCES IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHARMACOLOGY
1940

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CHARLES C. ROBY

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RELATIVE INCREASE IN CHLORIDE EXCRETION IN THE DOG AFTER GRADUATED DOSES OF MERCURIAL DIURETICS[1]

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Since mercurial diuretics are extensively used clinically to increase salt and water excretion, the purpose of this study was to find a more quantitative method of evaluating the chloride excretion produced by the organic mercurials and to determine any quantitative differences between these diuretics. Because mercurial diuretics increase urine flow by an inhibition of tubular function (1), it was thought probable that a range of dosage between minimum and maximum tubular inhibition could be determined for each mercurial. This range in dosage, as determined in dogs with bladder fistulae by increasing the dose of mercurial each week, would then represent the safe or "physiological range" of dosage and would be bounded on one extreme by the first evidence of increased chloride excretion and on the other extreme by the maximum chloride excretion obtained. The above approach would provide data on the physiological limits of chloride excretion which can be obtained with progressive tubular inhibition.

Experimental. Preliminary studies indicated that the total chloride excretion in milligrams of NaCl[2] would afford the most exact criterion of the total diuretic action. This was based on the finding that in order to obtain constant results, dehydrated animals must be used. Such animals, when injected with mercurial diuretics, frequently respond with a marked increase in chloride excretion, but no increase in water excretion. If urinary volume alone is used as a criterion of diuresis, many effective therapeutic responses would remain undetected.

The mercurial diuretics used in this study were: Salyrgan (N.N.R.), Mercurin (N.N.R.), the mercuric base of Esidrone (Na salt of pyridine-dicarboxymercuri-hydroxy-propylamide), and their corresponding Theophyllin-containing compounds, Salyrgan-Theophyllin solution (N.N.R.), Mercupurin (N.N.R.), and Esidrone.

Six groups of 5 dogs with bladder fistulae (2) were used in these studies. Experiments were performed by increasing weekly the mercurial dose in each group of 5 dogs. The animals were used only once a week to allow recovery of salt balance and to minimize the cumulative poisoning. The dogs were all well trained and unanesthetized. Water was withheld from them for 5 hours before they were placed in stocks, and a control period of 30 minutes was allowed, during

[1] Aided in part by a grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

[2] The product of the urinary volume and the milligram NaCl per cubic centimeter.

which time urine volume and chloride determinations (expressed as NaCl) were made every 10 minutes. At the end of the control period the diuretic drug was administered slowly, intravenously in a 1 to 3 cc. volume. Urine volume and chloride determinations were made thereafter every 10 minutes for 2 to 2½ hours. Inasmuch as this was also a study in chronic toxicity, the same approximate number of weekly doses was given to each group of animals. The increment of dosage was estimated from the therapeutic index[3] of each compound, so that each group of dogs received approximately 6 injections. In general, the experiments on each group of dogs were terminated when a larger dose of the mercurial diuretic produced a definite decrease in chloride excretion. Clinical methods of studying renal toxicity were not applicable in these dogs, for the exposed bladder wall frequently exudes mucin and red blood cells which invalidate the usual clinical tests. The results of these studies are tabulated in figure 1.

Discussion. Cardiac death (3) is known to occur with toxic doses of Salyrgan in the dog. The only cardiac deaths in this study occurred with Esidrone, where 2 dogs died after doses of 4 mgm. Hg/kgm. The addition of Theophyllin either in chemical combination (3 per cent in Mercupurin) or as a partial mixture (5 per cent in Salyrgan-Theophyllin solution) increases slightly the tolerated dose producing maximum inhibition and aids in reaching a higher peak of chloride excretion. All of the six groups of dogs showed a final decrease in chloride excretion with the highest dose used. This probably indicates that the physiological mechanism which accounts for this type of diuresis had been exceeded,—that is, the tubular inhibition had been superseded by tubular or glomerular damage.

Tubular damage (4) following repeated therapeutic doses of Novasurol has been observed. This was more marked following larger doses and disappeared if the drug was discontinued. In the 32 dogs given large doses of mercurials in these studies all of the kidneys were fixed one week after the last dose of mercury, and when stained with scarlet red, showed histological evidence of fatty degeneration of the tubules. There was also minimum fatty infiltration of the glomeruli at these toxic levels of dosage. No quantitative difference in kidney damage was noted; nor were any differences anticipated, since each group of dogs had been given a planned series of doses the last of which probably exceeded the point of maximum tubular inhibition as evidenced by the decreased chloride excretion obtained.

[3] Determined by intravenous rat toxicity and dog diuretic studies.

Fig. 1. The milligram chloride excretion, expressed as NaCl, has been corrected to a theoretical 10 kgm. dog (ordinates). Time is given in minutes (abscissae). Note that the doses of each mercurial have been increased stepwise until a larger dose produces a decreased chloride excretion. The abnormal range in control chloride excretions in the Salyrgan-Theophyllin solution graph may have been due to a high environmental temperature, as these experiments were performed in the late summer and early fall. Note the initial inhibition of chloride excretion with the mercuric base of Esidrone. Also note the speed of onset, the high level of chloride excretion, and the similarity of the curves obtained with Mercurin and Mercupurin. The addition of Theophyllin to Salyrgan and Esidrone results in an increase in chloride excretion.

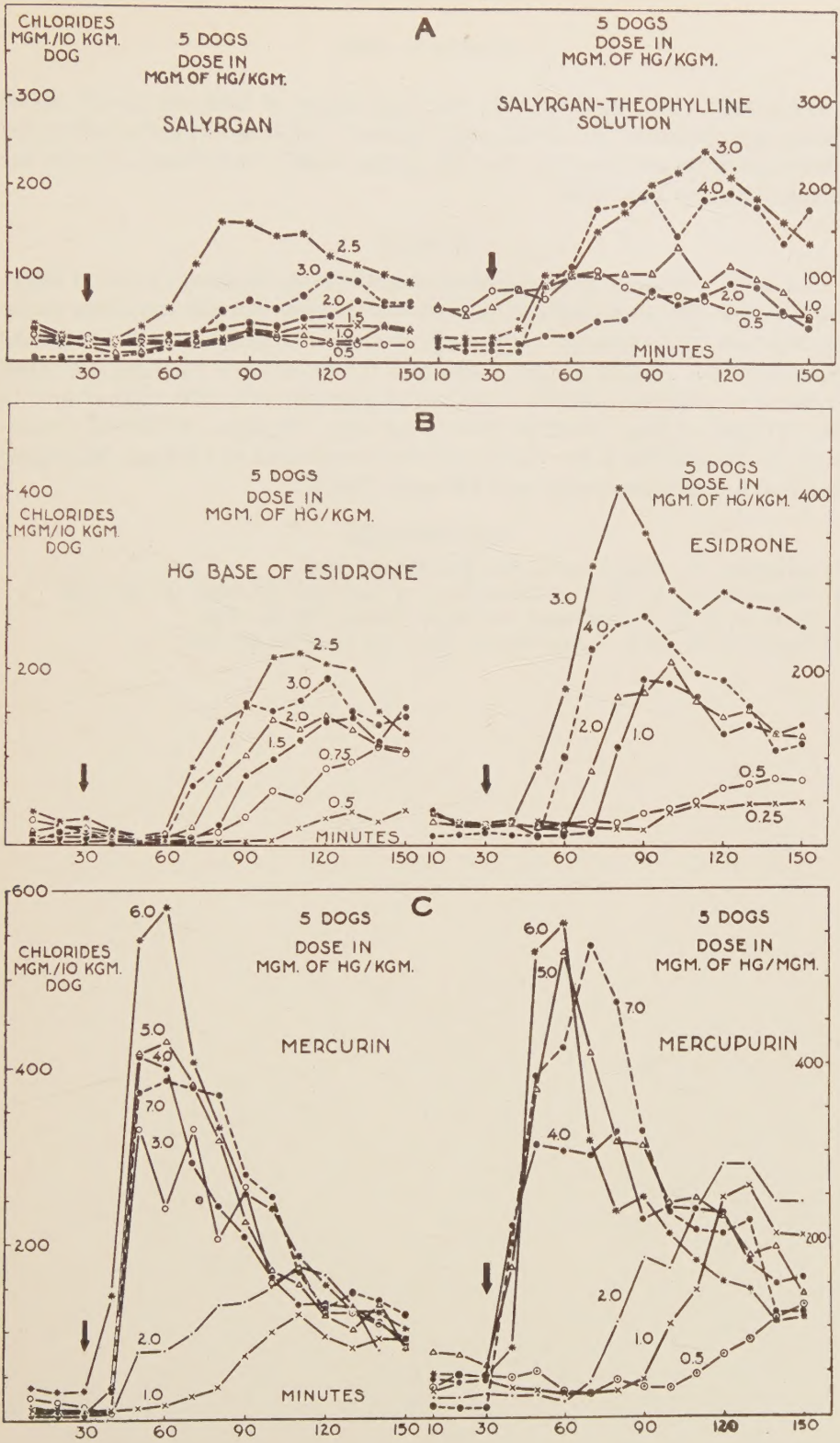
A
CHLORIDES MGM./10 KGM. DOG
5 DOGS DOSE IN MGM. OF HG/KGM.
SALYRGAN
5 DOGS DOSE IN MGM. OF HG/KGM.
SALYRGAN-THEOPHYLLINE SOLUTION
MINUTES
B
CHLORIDES MGM/10 KGM. DOG
5 DOGS DOSE IN MGM. OF HG/KGM.
HG BASE OF ESIDRONE
5 DOGS DOSE IN MGM. OF HG/KGM.
ESIDRONE
MINUTES
C
CHLORIDES MGM./10 KGM. DOG
5 DOGS DOSE IN MGM. OF HG/KGM.
MERCURIN
5 DOGS DOSE IN MGM. OF HG/MGM.
MERCUPURIN
MINUTES

Fig. 1

The deaths which occurred with the high dosage of Esidrone should advise against the continued use of this drug clinically until electrocardiographic and other studies are performed to rule out serious cardiac embarrassment with the clinical dose now employed.

SUMMARY

In a series of trained, unanesthetized dogs the range of dosage between beginning tubular inhibition and the maximum obtainable chloride excretion varies for each mercurial diuretic. This range is suggested as a means of evaluating these diuretics. Within a range of dosage of 0.5 to 2.5 mgm. Hg/kgm., Salyrgan produced a maximum chloride excretion of approximately 200 mgm. NaCl/10 min./10 kgm. of dog. Esidrone (0.5 to 3.0 mgm. Hg/kgm.) produced a maximum excretion of 300 mgm. NaCl, and Mercupurin (0.5 to 6.0 mgm. Hg/kgm.) produced a maximum excretion of 500 mgm. NaCl.

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